CLINICAL INVESTIGATIONS

Anesthesiology 1997; 87:6–17
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Permissive Hypercapnia with and without Expiratory Washout in Patients with Severe Acute Respiratory Distress Syndrome

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Background: Permissive hypercapnia is a ventilatory strategy aimed at avoiding lung volutrauma in patients with severe acute respiratory distress syndrome (ARDS). Expiratory washout (EWO) is a modality of trachcal gas insuffllation that enhances carbon dioxide removal during mechanical ventilation by reducing dead space. The goal of this prospective study was to determine the efficacy of EWO in reducing the partial pressure of carbon dioxide (Pco₂) in patients with severe ARDS treated using permissive hypercapnia.

Methods: Seven critically ill patients with severe ARDS (lung injury severity score, 3.1 ± 0.3) and no contraindications for permissive hypercapnia were studied. On the first day, hemodynamic and respiratory parameters were measured and the extent of lung hyperdensities was assessed using computed tomography. A positive end-expiratory pressure equal to the opening pressure identified on the pressure-volume curve was applied. Tidal volume was reduced until a plateau airway pressure of 25 cm H₂O was reached. On the second day, after implementation of permissive hypercapnia, EWO was instituted at a flow of 15 l/min administered during the entire inspiratory phase into the trachea through the proximal channel of an endotracheal tube using a ventilator equipped with a special flow generator. Cardiorespiratory parameters were studied under three conditions: permissive hypercapnia, permissive hypercapnia with EWO, and permissive hypercapnia.

Results: During permissive hypercapnia, EWO decreased Pco₂ from 76 ± 4 mmHg to 53 ± 3 mmHg (P < 0.001), increased pH from 7.20 ± 0.03 to 7.34 ± 0.04 (P < 0.001), and increased PaO₂ from 205 ± 28 to 296 ± 38 mmHg (P < 0.05). The reduction in Pco₂ was accompanied by an increase in end-inspiratory plateau pressure from 26 ± 1 to 32 ± 2 cm H₂O (P = 0.001). Expiratory washout also decreased cardiac index from 4.6 ± 0.4 to 3.7 ± 0.3 l/min⁻¹ m²⁻¹ (P < 0.01), mean pulmonary arterial pressure from 28 ± 2 to 25 ± 2 mmHg (P < 0.01), and true pulmonary shunt from 47 ± 2 to 36 ± 3% (P < 0.01).

Conclusions: Expiratory washout is an effective and easy-to-use ventilatory modality to reduce Pco₂ and increase pH during permissive hypercapnia. However, it significantly increases airway pressures and lung volume through expiratory flow limitation, reexposing some patients to a risk of lung volutrauma if the extrinsic positive end-expiratory pressure is not substantially reduced. (Key words: Hypercapnia. Lungs. Respiratory failure. Mechanical ventilation. Lung: acute respiratory distress syndrome.)

ACUTE respiratory distress syndrome (ARDS) is characterized by hypoxemia, high inflation pressures, increased pulmonary artery pressure, and the need for mechanical ventilation. Extensive use of thoracic computed tomography (CT) in patients with ARDS has pro-
vided compelling evidence for a substantial reduction in aerated lung parenchyma.\textsuperscript{1, 2} The resulting decreased lung compliance leads to high inflation pressures if a "normal" tidal volume (VT) is administered to ensure normocapnia.

Animal experiments have shown that VT of 40 ml/kg rapidly induces a high-permeability type of pulmonary edema.\textsuperscript{1, 2, 15} One histologic study performed in patients with severe ARDS showed that airspace enlargement, alveolar ruptures, emphysema-like lesions, pseudocyst formations—features characteristics of lung barotrauma—are enhanced by using large VTs, high airway pressures, and high fractional concentrations of oxygen in inspired gas ($F_{O_2}$).\textsuperscript{16} Conventional mechanical ventilation in patients with severe ARDS might induce, exacerbate, or perpetuate acute lung injury.\textsuperscript{7}

Deliberate reduction of VT resulting in permissive hypercapnia was recently advocated for reducing rates of morbidity and mortality related to ventilator-induced lung injury.\textsuperscript{8, 9} However, permissive hypercapnia has some drawbacks, such as an increase in pulmonary artery pressure, heart rate, cardiac index, and systemic arterial pressure through catecholamine release.\textsuperscript{10} It might also change the vasoactive status of regional vascular beds interfering with organ functions.\textsuperscript{11-14} Although in most critically ill patients these alterations are considered clinically unimportant,\textsuperscript{15} there is a consensus that permissive hypercapnia is contraindicated in patients with cerebral dysfunction, coronary artery disease, and severe metabolic acidosis.

Any ventilatory modality that would permit a reduction in the partial pressure of carbon dioxide ($P_{aCO_2}$) while maintaining low VT would be a significant improvement. Insufflation of fresh gas directly into the trachea or bronchi through catheters was first described in apneic dogs to maintain sufficient gas exchange to support life over prolonged periods.\textsuperscript{16-19} Later tracheal gas insufflation (TGI), as an adjunct to mechanical ventilation, was developed.\textsuperscript{20-24} In addition to the VT delivered by the ventilator, fresh gas is insufflated directly into the trachea, either continuously during the entire ventilatory cycle (continuous flow), during the inspiratory phase only (inspiratory bypass), or during the expiratory phase only (expiratory washout [EWO]). The ability of TGI to reduce $P_{aCO_2}$ is based on a decrease in the dead space to tidal volume ratio. If administered during the entire expiratory phase and at a sufficient flow rate, EWO is more efficient than inspiratory bypass in reducing $P_{aCO_2}$.\textsuperscript{22} Recently, EWO was used to reduce dead space in premature neonates, in whom respiratory tubings contribute significantly to the increased total dead space during mechanical ventilation.\textsuperscript{25}

This prospective study was undertaken to assess the efficacy of EWO for reducing $P_{aCO_2}$ and to quantify its effects on airway pressures in patients with severe ARDS treated by a ventilatory strategy based on permissive hypercapnia.

### Materials and Methods

#### Patients

During a 14-month period, 34 consecutive patients with ARDS diagnosed at the time of or after admission to the surgical intensive care unit (Department of Anesthesiology) of La Pitié-Salpêtrière Hospital (Paris, France) were prospectively assessed for inclusion in the study. Written informed consent was obtained from each patient's next of kin. The study was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomedicale de la Hospital Pitié-Salpêtrière. Inclusion criteria were (1) bilateral infiltrates on a bedside chest radiograph and bilateral and extensive hyperdensities on a high-resolution spiral thoracic CT scan; (2) pulmonary capillary wedge pressure less than 18 mmHg and lack of left ventricular dysfunction as assessed by transesophageal echocardiography; (3) $P_{aCO_2}$ more than 50 mmHg using the following ventilatory settings with the patient sedated and paralyzed: volume-controlled mode with VT regulated to attain a plateau airway pressure of 25 cm H$_2$O, respiratory rate of 18 breaths per minute, and positive end-expiratory pressure (PEEP) of 10 cm H$_2$O. These inclusion criteria were intended to identify patients with severe ARDS at risk for mechanical ventilation-induced lung volutrauma in whom a pressure- and volume-limited ventilatory strategy was indicated. The pressure target of 25 cm H$_2$O was based on a recent study showing that the upper inflection pressure identified on the pressure-volume (PV) curve was 26 ± 6 cm H$_2$O in a series of patients with ARDS and that the administration of a VT of 10 ml/kg resulted in a plateau airway pressure greater than the upper distending pressure in 80% of them.\textsuperscript{26} Exclusion criteria were head injury, intracranial space-occupying lesions; severe hypertensive disease; and acute coronary insufficiency. These criteria were in-

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tended to exclude patients in whom permissive hypercapnia could induce detrimental effects on cerebral and coronary blood flows.

Seven patients fulfilling inclusion and exclusion criteria were included in the study. In each patient, the trachea was orally intubated using a Hi-Lo Jet number 8 Mallinckrodt tube (Mallinckrodt Inc., Argyle, NY) that incorporates two side ports, one ending at the distal tip of the endotracheal tube and a more proximal port ending 6 cm from the tip. These additional channels were used for continuous monitoring of tracheal pressure (distal channel) and for EWO administration (proximal channel). After inclusion in the study, all patients were sedated and paralyzed with a continuous intravenous infusion of 250 mg/h fentanyl, 1 mg/h fentanyl, 4 mg/h vecuronium. The lungs were ventilated using a César ventilator (Taema; Antony, France) set in conventional volume-controlled mode. In all patients, hemodynamics were monitored using a fiberoptic thermodilution pulmonary artery catheter (CCO/SvO₂/VIP TD catheter; Baxter Healthcare, Irvine, CA) and a radial or femoral arterial catheter.

High-Resolution and Spiral Thoracic Computed Tomographic Scan

To assess the severity of ARDS, extension of lung hyperdensities was quantified on a thoracic CT scan. The anesthetized and paralyzed patient was transported to the radiology department (thoracic division) and scanning was performed from the apex of the lungs to the diaphragm (using a Tomoscan SR 7000; Philips, Eindhoven, The Netherlands). All images were observed and photographed at a window width of 1,000 HU (Hounsfield units) and a level of 700 HU. Evaluation included high-resolution thin-section CT and spiral CT in all patients. The thin-section CT examination consisted of a series of 1.5-mm-thick sections with 20-mm intersection spacing selected using a thoracic scout view during a 25-s period of apnea, with the tracheal tube disconnected from the ventilator (pulmonary volume equal to apneic functional residual capacity). For spiral CT, 10-mm-thick contiguous axial sections were reconstructed from the volumetric data obtained during a 15-s period of apnea. During transportation to the radiology department, and throughout the CT scan procedure, mechanical ventilation was provided using an Osiris ventilator (Taema) delivering 100% oxygen, and cardiovascular monitoring was ensured using a Propaq 10i EL monitor (Protocol System, North Chicago, IL), which allowed continuous monitoring of pulse oximetry, systemic and pulmonary arterial pressures, and electric activity of the heart. A semiquantitative CT assessment of parenchymal hyperdensities at zero end-expiratory pressure was performed according to a previously described technique.²⁷

Measurements

Systemic arterial pressure and pulmonary arterial pressure were measured simultaneously using the arterial cannula and the fiberoptic pulmonary artery catheter connected to two calibrated pressure transducers (91 DPT-308, Mallinckrodt) positioned at the midaxillary line. Tracheal pressure was measured using the distal channel of the endotracheal tube connected to a third calibrated pressure transducer (91 DPT-308, Mallinckrodt). At the end of each phase, these signals were recorded at a high sample rate of 100 Hz on a data acquisition and analysis system including a MP100 WS (Biopac Systems, Goleta, CA) data acquisition system and a Quadra 610 Macintosh computer (Apple Computers, Cupertino, CA) connected to the analog port of the hemodynamic monitor Merlin (Hewlett-Packard, Palo Alto, CA). Using the software package AcqKnowledge included in the MP100 WS system, heart rate, mean arterial pressure, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, right atrial pressure, mean tracheal pressure, and end-inspiratory plateau pressure were measured. Cardiac output was measured using the semicontinuous thermodilution technique (CCO/SvO₂/VIP TD catheter).²⁸ Systemic and pulmonary arterial blood samples were withdrawn simultaneously and arterial pH, partial pressure of oxygen (Pao₂), partial pressure of oxygen in mixed venous blood (PvO₂), and PaCO₂ were measured using an IL BGE blood gas analyzer (Instrumentation Laboratory, Paris, France). Hemoglobin concentration and arterial and mixed venous oxygen saturations (SaO₂ and SvO₂) were measured using a calibrated OSM3 hemoximeter (Radiometer Copenhagen, Neuilly-Plaisance, France). Standard formulas were used to calculate cardiac index, pulmonary vascular resistance index, systemic vascular resistance index, right ventricular stroke work index, true pulmonary shunt, arteriovenous oxygen difference, oxygen delivery, oxygen consumption, and oxygen extraction ratio.

Respiratory PV curves were obtained as follows: the endotracheal tube was disconnected from the ventilator

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to allow functional residual capacity to be reached; then the lungs were inflated using a 1-L syringe (Model Series 5540, Hans Rudolph, Kansas City, MO) filled with oxygen in increments of 50 ml from 0 to 500 ml and increments of 100 ml from 500 to 1,000 ml with a 1.5-s pause at the end of each inflation. Airway pressure was recorded on a Gould ES 1000 recorder (Gould Instruments, Cleveland, OH) to determine the opening pressure. Static respiratory compliance was calculated as the slope of the PV curve in its linear part. Quasi-static respiratory compliance was determined by dividing the VT of the patient by the corresponding airway pressure on the P-V curve. In patients with auto-PEEP, P-V curves were normalized by subtracting the value of auto-PEEP from each value of airway pressure.

In each patient, expired carbon dioxide was measured using a nonaspirative calibrated 47210A infrared capnometer (Hewlett-Packard, Andover, MA) positioned between the proximal end of the endotracheal tube and the Y-piece of the ventilator. Expiratory carbon dioxide curves were recorded on the MP100 WS data acquisition system. After simultaneously withdrawing an arterial blood sample, the ratio of alveolar dead space (V_{A0}) to VT was calculated according the following equation:

\[ V_{A0}/VT = 1 - \text{PETCO}_2/\text{PaCO}_2 \]

where PETCO₂ is end-tidal carbon dioxide measured at the plateau of the expired carbon dioxide curve. Only tracings demonstrating a clear end-expiratory plateau were used to determine PETCO₂. Because EWO markedly interfered with expired CO₂ curve, V_{A0}/VT was calculated only during control experiments without EWO. Because acute lung injury is often associated with vascular abnormalities of the pulmonary circulation (local thrombi and pulmonary vasoconstriction), V_{A0}/VT is a better index of these vascular lesions than physiologic dead space calculated using the Bohr equation, which accounts for the anatomic dead space.²⁹

**Expiratory Washout Administration**

The ventilator used for the study was equipped with a specific additional flow generator providing EWO. The nebulization software function incorporated in the César ventilator was used to synchronize EWO flow (with the same F_{O2} as inspired gas) with the expiratory phase. Expiratory washout was carried out during the entire expiratory phase. The EWO flow was measured using a calibrated pneumotacograph incorporated in the additional flow generator. An analog knob on the front panel of the additional flow generator permitted the administration of the EWO flow in a range of 0 to 15 l/min. An EWO flow of 15 l/min was selected and delivered through the proximal channel of the endotracheal tube itself connected to the additional flow generator by a 3 mm-internal diameter connecting tube (Argyle; Sherwood Medical, Tullamore, Ireland; fig. 1).

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*Fig. 1. The prototype ventilator equipped with expiratory washout (EWO). (A) End-expiration without EWO. (B) End-expiration with EWO 15 l/min: carbon dioxide has been removed entirely from “prosthetic” dead space. In addition, a distal washout effect is shown below the distal tip of the EWO channel of the endotracheal tube (see comments in the discussion). 1 = César ventilator, 2 = connecting tube between the Y-piece and the endotracheal tube, 3 = Mallinckrodt Hi-Lo Jet endotracheal tube, 4 = EWO prototype connected to the proximal channel of the endotracheal tube, Paw = distal channel of the endotracheal tube that allows airway pressure monitoring.*
**Protocol**

The study was performed during a 2-day period. On the first day, the protocol consisted of verifying inclusion and exclusion criteria, and obtaining initial hemodynamic and respiratory measurements and PV curves at zero end-expiratory pressure and a \( F_{1O_2} \) of 1. Then a high-resolution and spiral thoracic CT scan was performed and permissive hypercapnia was implemented according to the following rationale: a PEEP equal to the opening pressure visually assessed on the P-V curve was administered, respiratory rate and I/E ratio were set at 18 breaths per minute and 33%, respectively; and VT was reduced to obtain an end-expiratory plateau pressure of 25 cm H\(_2\)O. If Pa\(_{CO_2}\) was more than 110 mmHg with these ventilatory settings, respiratory rate was increased to more than 18 breaths per minute to decrease Pa\(_{CO_2}\).

On the second day, the study consisted of three phases, with an overall duration ranging from 4 to 6 h. At the end of each phase and after a 60-min steady state was obtained, hemodynamic and respiratory measurements were performed. In phase 1, permissive hypercapnia without EWO, the patient was ventilated without EWO at the ventilatory settings determined and initiated on day 1. In phase 2, permissive hypercapnia with EWO, the same ventilatory settings were maintained and a 15L/min EWO was administered through the proximal part of the endotracheal tube during the entire expiratory phase. In phase 3, permissive hypercapnia without EWO, the same ventilatory settings were maintained and EWD administration was stopped.

**Statistical Analysis**

All data are presented as means ± SEM. Probability values less than 0.05 were considered significant. A one-way analysis of variance was performed followed by the Bonferroni multiple comparison test. Changes in mean tracheal pressure and Pa\(_{CO_2}\) were compared using linear regression analysis.

**Results**

**Patients**

Table 1 presents the initial individual clinical characteristics, recorded on the day of inclusion into the study. In five patients ARDS was observed after major surgery, and in one patient it was seen after severe trauma. Four patients were included in the study during the first week of their ARDS, whereas three were included at a later stage. Among the seven patients studied, six had circulatory shock, defined as a systolic arterial pressure less than 90 mmHg or dependence on exogenous catecholamines. Table 2 shows the initial respiratory and hemodynamic characteristics during volume-controlled mode of ventilation \( F_{1O_2} \), 1.0; zero end-expiratory pressure). Five patients were classified as having severe ARDS according to the recommendations of the American-European Consensus Conference on ARDS. Patients 1 and 4, who were not severely hypoxemic, had extensive lung hyperdensities (53% and 40% of total lung volume, respectively) requiring a low VT to obtain an end-inspiratory plateau pressure of 25 cm H\(_2\)O at control. All patients had a low static respiratory compliance (38 ± 2 ml/cm H\(_2\)O); in four of them, an upper inflection pressure could be visually identified, indicating that above this pressure, lung overdistention was likely to occur. After the reduction in VT, all patients had high Pa\(_{CO_2}\) levels (76 ± 4 mmHg) associated with respiratory acidosis (pH = 7.20 ± 0.03).

**Hemodynamic and Respiratory Changes**

Tables 3 and 4 summarize hemodynamic and respiratory data measured during permissive hypercapnia with and without EWO.

**Effects of Expiratory Washout on Gas Exchange.**

During patient-adapted permissive hypercapnia, the administration of 15 L/min EWO resulted in a significant decrease in Pa\(_{CO_2}\) from 76 ± 4 mmHg to 53 ± 3 mmHg \((P < 0.0001)\) and a significant increase in pH from 7.20 ± 0.03 to 7.34 ± 0.04. With EWO, Pa\(_{CO_2}\) decreased from baseline in every patient (range of reduction, −27% to −34%; fig. 2). Before EWO and after EWO, Pa\(_{CO_2}\) was not significantly different for permissive hypercapnia. Expiratory washout also induced a significant increase in Pa\(_{O_2}\) from 205 ± 29 mmHg to 296 ± 38 mmHg \((P < 0.05)\). A highly significant correlation was found between changes in Pa\(_{O_2}\) and change in mean tracheal pressure \((r = 0.99; P < 0.0001)\).

**Effects of Expiratory Washout on Tracheal Pressures.**

The reduction in Pa\(_{CO_2}\) induced by EWO was accompanied in each patient by significant increases in end-inspiratory plateau pressure and mean tracheal pressure, of +26% and +29%, respectively \((P < 0.0001)\). There was no significant difference in tracheal pressures between phase 1 (permissive hypercapnia be-
PERMISSIVE HYPERCAPNIA AND TRACHEAL EXPIRATORY WASHOUT

Table 1. Initial Clinical Characteristics of the Seven Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>SAPS 2</th>
<th>LISS</th>
<th>Cause of ARDS</th>
<th>% of lung hyperdensities at ZEEP</th>
<th>Delay from onset (days)</th>
<th>Septic shock</th>
<th>COPD</th>
<th>Delay to discharge/death (days)</th>
<th>Outcome</th>
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<td>2</td>
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<td>yes</td>
<td>11</td>
<td>D</td>
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</table>

M = male; F = female; SAPS 2 = simplified acute physiologic score; LISS = lung injury severity score; ARDS = adult respiratory distress syndrome; ZEEP = zero end expiratory pressure; nBPN = nosocomial bronchopneumonia; aspPN = aspiration pneumonia; Ph Car PN = pneumonia caused by Pneumocystis carinii; COPD = chronic obstructive pulmonary disease; S = survived; D = deceased.

Table 2. Initial Individual Respiratory and Hemodynamic Parameters with $F_{O_{2}} 1$, ZEEP

| Patient | VT (ml) | RR (breaths·min⁻¹) | MV (L·min⁻¹) | $P_{aO_2}$ (mmHg) | $P_{aCO_2}$ (mmHg) | pH | $P_{aCO_2}$ (cmH₂O) | $P_{v_{a}/VT}$ | $Q_{O_2}/Q_{c}$ (%) | CI (L·min⁻¹·m⁻²) | HR (beats·min⁻¹) | MAP (mmHg) | MPAP (mmHg) | PCWP (mmHg) | RAP (mmHg) | SVRI (dynes·s·cm⁻⁵·m⁻²) | PVRI (dynes·s·cm⁻⁵·m⁻²) | Mean ± SEM |
|---------|---------|-------------------|--------------|-------------------|-------------------|----|---------------------|----------------|---------------------|----------------|----------------|------------|-------------|-----------|-----------|-------------|-----------|--------------------------|--------------------------|------------|
| 1       | 940     | 18                | 17           | 349               | 46                | 7.41 | 43                  | 32             | 38                  | 8             | 100           | 75         | 16         | 5          | 2         | 1,615       | 240        | 679 ± 51   |
| 2       | 770     | 18                | 14           | 240               | 49                | 7.41 | 27                  | 37             | 37                  | 8             | 100           | 75         | 16         | 5          | 2         | 1,303       | 270        | 1,407 ± 152|
| 3       | 580     | 20                | 12           | 73                | 48                | 7.34 | 21                  | 26             | 26                  | 10            | 100           | 75         | 16         | 5          | 2         | 2,096       | 370        | 1,141      |
| 4       | 610     | 18                | 11           | 354               | 41                | 7.45 | 28                  | 31             | 35                  | 10            | 100           | 75         | 16         | 5          | 2         | 730         | 370        | 1,367      |
| 5       | 560     | 18                | 10           | 73                | 43                | 7.26 | 34                  | 32             | 40                  | 10            | 100           | 75         | 16         | 5          | 2         | 1,502       | 408        | 1,141      |
| 6       | 680     | 20                | 14           | 69                | 40                | 7.36 | 31                  | 22             | 43                  | 10            | 100           | 75         | 16         | 5          | 2         | 1,367       | 271        | 1,407 ± 152|
| 7       | 610     | 18                | 11           | 69                | 49                | 7.33 | 31                  | 22             | 43                  | 10            | 100           | 75         | 16         | 5          | 2         | 1,141       | 271        | 1,407 ± 152|

VT = tidal volume; RR = respiratory rate; MV = minute ventilation; $P_{max}$ = peak inspiratory tracheal pressure; $P_{iv}$ = end-inspiratory plateau tracheal pressure; $C_{rs}$ = quasistatic respiratory compliance; $C_{st}$ = static respiratory compliance; $P_{o_{2}}$ = opening pressure; $V_{a}/VT$ = alveolar dead space to tidal volume ratio; $Q_{O_{2}}/Q_{c}$ = cardiac index; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; SVRI = systemic vascular resistance index; PVRI = pulmonary vascular resistance index; ZEEP = zero end expiratory pressure.

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Table 3. Respiratory and Metabolic Parameters Measured during the Three Phases of the Study

<table>
<thead>
<tr>
<th></th>
<th>PH</th>
<th>PH + EWO</th>
<th>PH Control</th>
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<th>PH + EWO versus PH Control (P)</th>
<th>PH versus PH Control (P)</th>
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<tr>
<td>VT (ml)</td>
<td>414 ± 27</td>
<td>414 ± 27</td>
<td>414 ± 27</td>
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<td>RR (breaths · min⁻¹)</td>
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<td>MV (L · min⁻¹)</td>
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<td>NS</td>
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<tr>
<td>P&lt;sub&gt;max,VT&lt;/sub&gt; (cmH₂O)</td>
<td>31 ± 1</td>
<td>37 ± 2</td>
<td>29 ± 1</td>
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<td>P&lt;sub&gt;ET,CO₂&lt;/sub&gt; (cmH₂O)</td>
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<td>32 ± 2</td>
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<td>M&lt;sub&gt;p&lt;/sub&gt; (cmH₂O)</td>
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<td>18 ± 1</td>
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<tr>
<td>P&lt;sub&gt;ACO₂&lt;/sub&gt; (mmHg)</td>
<td>76 ± 4</td>
<td>53 ± 3</td>
<td>77 ± 5</td>
<td>&lt;0.001</td>
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<td>pH</td>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
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<tr>
<td>P&lt;sub&gt;A&lt;/sub&gt;CO₂ (mmHg)</td>
<td>205 ± 28</td>
<td>296 ± 38</td>
<td>236 ± 31</td>
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</tr>
<tr>
<td>V&lt;sub&gt;VT&lt;/sub&gt;VT (%)</td>
<td>32 ± 2</td>
<td>ND</td>
<td>30 ± 3</td>
<td>—</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>C(a-v)O₂ (vol/100 ml)</td>
<td>1.9 ± 0.3</td>
<td>2.5 ± 0.2</td>
<td>2.0 ± 0.5</td>
<td>0.001</td>
<td>0.001</td>
<td>NS</td>
</tr>
<tr>
<td>D&lt;sub&gt;M&lt;/sub&gt; (ml · min⁻¹ · m⁻²)</td>
<td>518 ± 49</td>
<td>451 ± 39</td>
<td>514 ± 55</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>V&lt;sub&gt;CO₂&lt;/sub&gt; (ml · min⁻¹ · m⁻²)</td>
<td>87 ± 7</td>
<td>94 ± 8</td>
<td>86 ± 8</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>E&lt;sub&gt;A&lt;/sub&gt;O₂ (%)</td>
<td>17 ± 1</td>
<td>21 ± 2</td>
<td>17 ± 1</td>
<td>0.001</td>
<td>0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Q&lt;sub&gt;O&lt;/sub&gt;/Q&lt;sub&gt;l&lt;/sub&gt; (%)</td>
<td>47 ± 2</td>
<td>36 ± 3</td>
<td>47 ± 2</td>
<td>0.001</td>
<td>0.001</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Statistical analysis was performed using a one-way analysis of variance followed by a Bonferroni multiple comparison test.

PH = permissive hypercapnia; PH + EWO = permissive hypercapnia with expiratory washout; PH Control = permissive hypercapnia; VT = tidal volume; RR = respiratory rate; MV = minute ventilation; P<sub>max,VT</sub> = peak inspiratory tracheal pressure; P<sub>ET,CO₂</sub> = end-inspiratory plateau tracheal pressure; M<sub>p</sub> = mean tracheal pressure; P<sub>T</sub>CO₂ = end-tidal fraction of carbon dioxide; V<sub>VT</sub>VT = alveolar dead space to tidal volume ratio; C(a-v)O₂ = arteriovenous oxygen difference; D<sub>M</sub> = oxygen delivery; V<sub>CO₂</sub> = oxygen consumption; E<sub>A</sub>O₂ = oxygen extraction ratio; Q<sub>O</sub>/Q<sub>l</sub> = true pulmonary shunt; ND = not determined; NS = not significant.

fore EWO) and phase 3 (permissive hypercapnia after EWO). In three of the four patients in whom an upper inflection pressure was identified on the PV curve, the end-inspiratory plateau pressure during EWO exceeded this upper inflection pressure.

**Effects of Expiratory Washout on Hemodynamic and Metabolic Parameters.** EWO decreased cardiac index by 20% (**P = 0.004**), heart rate by 9% (**P = 0.03**), mean pulmonary arterial pressure by 11% (**P = 0.005**), right ventricular stroke work index by 25% (**P = 0.0003**),

Table 4. Hemodynamic Parameters Measured during the Three Phases of the Study

<table>
<thead>
<tr>
<th></th>
<th>PH</th>
<th>PH + EWO</th>
<th>PH Control</th>
<th>PH + EWO versus PH Control (P)</th>
<th>PH + EWO versus PH Control (P)</th>
<th>PH versus PH Control (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl (L · min⁻¹)</td>
<td>4.6 ± 0.4</td>
<td>3.7 ± 0.3</td>
<td>4.5 ± 0.4</td>
<td>0.01</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>HR (beats · min⁻¹)</td>
<td>103 ± 8</td>
<td>94 ± 7</td>
<td>105 ± 7</td>
<td>0.01</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>SVI (ml · m⁻²)</td>
<td>45 ± 3</td>
<td>40 ± 3</td>
<td>45 ± 3</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>72 ± 5</td>
<td>73 ± 5</td>
<td>77 ± 5</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MPAP (mmHg)</td>
<td>28 ± 2</td>
<td>25 ± 2</td>
<td>29 ± 2</td>
<td>0.01</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>RVS (g · m⁻²)</td>
<td>12 ± 1</td>
<td>9 ± 1</td>
<td>11 ± 1</td>
<td>0.01</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>9 ± 2</td>
<td>9 ± 2</td>
<td>10 ± 2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>11 ± 2</td>
<td>11 ± 2</td>
<td>12 ± 2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PVRI (dynes · s · cm⁻³ · m⁻²)</td>
<td>325 ± 41</td>
<td>318 ± 39</td>
<td>315 ± 40</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SVRI (dynes · s · cm⁻³ · m⁻²)</td>
<td>1,151 ± 126</td>
<td>1,407 ± 120</td>
<td>1,235 ± 148</td>
<td>0.01</td>
<td>0.01</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Statistical analysis was performed using a one-analysis variance followed by a Bonferroni multiple comparison test.

PH = permissive hypercapnia; PH + EWO = permissive hypercapnia with expiratory washout; PH Control = permissive hypercapnia; Cl = cardiac index; HR = heart rate; SVI = systolic volume index; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; RVS = right ventricular stroke volume index; RAP = right atrial pressure; PCWP = pulmonary capillary wedge pressure; PVRI = pulmonary vascular resistance index; SVRI = systemic vascular resistance index.

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\[
\text{PaCO}_2 (\text{mmHg})
\]

\[\begin{array}{ccc}
\text{PH} & \text{PH + EWO} & \text{PH control} \\
100 & 95 & 85 \\
85 & 80 & 70 \\
70 & 65 & 60 \\
60 & 55 & 50 \\
55 & 50 & 45 \\
50 & 45 & 40 \\
45 & 40 & 35 \\
40 & 35 & 30 \\
35 & 30 & 25 \\
30 & 25 & 20 \\
25 & 20 & 15 \\
20 & 15 & 10 \\
15 & 10 & 5 \\
10 & 5 & 0 \\
\end{array}\]

Fig. 2. Individual changes in \(\text{PaCO}_2\) during permissive hypercapnia (PH) and PH + expiratory washout (EWO) in seven patients with severe acute respiratory distress syndrome.

and true pulmonary shunt by 24\% (\(P = 0.003\)). EWO increased the systemic vascular resistance index by 22\% (\(P = 0.003\)), the arteriovenous oxygen difference by 32\% (\(P = 0.004\)), and the oxygen extraction ratio by 29\% (\(P = 0.02\)). Figure 3 shows comparative variations of \(\text{PaO}_2\) and true pulmonary shunt.

**Discussion**

This study, performed in a series of patients with severe ARDS, in whom a strategy of permissive hypercapnia was implemented to limit the risk of mechanical ventilation-induced volutrauma, shows that an EWO of 15 l/min reduced \(\text{PaCO}_2\) by 30\% and increased arterial \(p\text{H}\); increased \(\text{PaO}_2\) by 44\% and reduced pulmonary shunt by 24\%; and significantly reduced cardiac index, heart rate, and pulmonary arterial pressure. However, these potential beneficial cardiorespiratory effects were associated with an increase in plateau and mean airway pressures of 26\% and 29\%, respectively, reintroducing a risk of lung barotrauma in three of the patients.

**Characteristics of the study population**

All patients included in the study had severe ARDS characterized by extensive alveolar hyperdensities involving at least 40\% of lung parenchyma and major alterations of respiratory mechanics resulting in static compliance of 46 ml/cm \(H_2O\) or less. As a consequence, the VT required for limiting plateau airway pressure at a value of 25 cm \(H_2O\) was always low, ranging from 4-6 ml/kg. Severe hypoxemia, defined as a \(\text{PaO}_2/\text{FiO}_2\) less than 150 mmHg, which reflects ventilation perfusion mismatch rather than extension of the alveolar disease, was observed only in four patients. Other researchers have recently shown that the severity of oxygenation defect in patients with acute lung injury cannot be considered as a good predictive factor of death and severity of ARDS, perhaps because the degree of hypoxemia depends on several parameters, such as sedation, oxygen consumption, cardiac output, PEEP-induced alveolar recruitment, efficacy of hypoxic pulmonary vasoconstriction, and administration of selective pulmonary vasodilators and vasoconstrictors.

In the present investigation, we studied homogeneous series of patients at risk for mechanical ventilation-induced lung volutrauma, all of whom had extensive acute lung injury and elevated airway pressure.

\[
\text{Qs/Qt} (\%) \quad \text{PaO}_2 (\text{mmHg})
\]

\[\begin{array}{ccc}
\text{PH} & \text{PH + EWO} & \text{PH control} \\
52 & 48 & 36 \\
48 & 44 & 40 \\
44 & 40 & 36 \\
40 & 36 & 30 \\
36 & 30 & 25 \\
30 & 25 & 20 \\
25 & 20 & 15 \\
20 & 15 & 10 \\
15 & 10 & 5 \\
10 & 5 & 0 \\
\end{array}\]

Fig. 3. Changes in \(\text{PaO}_2\) and true pulmonary shunt (Qs/Qt) during permissive hypercapnia (PH) and PH + expiratory washout (EWO) in seven patients with severe acute distress syndrome (mean + SEM, *\(P < 0.05\)).
Effects of Expiratory Washout on Carbon Dioxide Elimination

An EWO of 15 l/min was effective in reducing \( \text{Pa}_{\text{CO}_2} \) by 30% and reversing permissive hypercapnia-induced acute respiratory acidosis. This is the first demonstration of the efficacy of EWO in reducing \( \text{Pa}_{\text{CO}_2} \) in patients with severe ARDS treated by permissive hypercapnia. Previous studies have shown that a 4-6 l/min continuous flow delivered into the trachea via a catheter positioned close to the carina could induce a 15-25% decrease in \( \text{Pa}_{\text{CO}_2} \) in patients with various forms of acute respiratory failure.\(^{21,35-37} \) In these studies, minute ventilation was maintained at a constant level by reducing VT, and the improvement in carbon dioxide elimination was attributed to the washout of the carbon dioxide-laden gas present in the anatomical dead space. In the present study, VT and minute ventilation were deliberately reduced before EWO administration, resulting in a markedly higher basal \( \text{Pa}_{\text{CO}_2} \) level.

The main mechanism by which the high-flow EWO reduced \( \text{Pa}_{\text{CO}_2} \) was probably the removal of the carbon dioxide-laden gas occupying the endotracheal tube located above the distal orifice of the proximal channel and the connecting piece between the endotracheal tube and the Y-piece ("mechanical" dead space). Similar to what happens during high-frequency ventilation, the interface between the fresh inspiratory gas and the carbon dioxide-laden expiratory gas was brought to the distal part of the endotracheal tube instead of the Y-piece, thereby decreasing the VD/VT ratio.\(^{38} \) An experimental study has shown that \( \text{Pa}_{\text{CO}_2} \) is reduced more when high-flow EWO is applied during the entire expiratory phase compared with inspiratory bypass delivered into the trachea.\(^{22} \) This result suggests that high-flow EWO applied during the entire expiratory phase induces fresh gas projections beyond the site of administration that removes carbon dioxide from a greater volume than the mechanical dead space. This hypothesis was confirmed by an experimental study using two types of catheters — straight and inverted — to deliver fresh gas into the trachea of healthy dogs.\(^{39} \)

Based on these previous observations, we chose to deliver the EWO in a straight direction to obtain additional distal washout effects. According to the ventilatory settings used, an EWO of 15 l/min resulted in a flush volume of 515 ml, which is six times higher than the 80 ml volume of mechanical dead space. Consequently, turbulence may have been generated at the distal tip of the proximal channel, enhancing carbon dioxide elimination by removing carbon dioxide-laden gas from a portion of the tracheobronchial tree.\(^{39} \)

In ARDS, the increased alveolar dead space reduces the ability of TGI to improve carbon dioxide elimination because end-tidal carbon dioxide decreases in ventilated but poorly perfused lung areas, and the same washout effect removes a smaller amount of carbon dioxide.\(^{22,40} \) Permissive hypercapnia has the opposite effect because it increases end-tidal carbon dioxide. In a recent canine model of lung injury with conditions very similar to those of the present clinical study (high-flow EWO, acute lung injury, permissive hypercapnia), Nahum et al.\(^{41} \) found a 30% reduction in \( \text{Pa}_{\text{CO}_2} \) after the implementation of a 101/min flow EWO. In fact, carbon dioxide rebreathing has a greater effect on \( \text{Pa}_{\text{CO}_2} \) in hypercapnic conditions compared with normocapnia. By washing out high concentrations of carbon dioxide present in the endotracheal tube, connecting pieces, and tracheobronchial tree, EWO is more efficient in permissive hypercapnia resulting from deliberate reduction of tidal volume than in conventional normocapnic ventilation.

Effects of Expiratory Washout on Airway Pressure

The significant increase in airway pressure and lung volume induced by EWO should be considered a side effect of this new ventilatory modality and appears to depend on EWO flow.\(^{39} \) We selected a high EWO flow to obtain the maximal distal effect on carbon dioxide removal. During TGI, high flow may induce increases in lung volume and airway pressure that are not detected by standard in-ventilator pressure measurements.\(^{21,22,25,36,41} \) In the present study, monitoring of tracheal pressure beyond the site of EWO administration revealed a 26% EWO-induced increase in plateau airway pressure that may have been related to expiratory flow limitation with subsequent development of auto-PEEP. From a practical point of view, measurement of EWO-induced intrinsic PEEP requires exact synchronization between suppression of EWO and occlusion of the expiratory valve, to avoid hyperinflation induced by persistent flow during the occlusive maneuver. The prototype that we used was not equipped with a system allowing such an occlusive maneuver. As a consequence, EWO-induced auto-PEEP and the corresponding increase in lung volume could not be measured. In the future, it is clear from the present data that any ventilator providing
PERMISSIVE HYPERCAPNIA AND TRACHEAL EXPIRATORY WASHOUT

TGI and EWO should have a provision for manual or automatic occlusive maneuvers that would allow measurement of intrinsic PEEP.

The increase in airway pressure resulting from EWO-induced expiratory flow limitation may reintroduce a risk of lung barotrauma. In three patients, the end-inspiratory plateau pressure measured during EWO exceeded the upper inflection pressure determined on the PV curve, therefore reintroducing a potential risk of volutrauma. Three different approaches can be used to limit the increase in airway pressure during EWO. The simplest method is to reduce the EWO flow. A 10-l/min EWO induces a significant 25% decrease in $P_{a_{CO_2}}$ with an increase in airway pressure that was either not detectable or less than 3 cm H$_2$O (personal data not shown). Another method consists of applying EWO during the later part of the expiratory phase, as already proposed by different authors, to allow the lung to return close to its end-expiratory lung volume before EWO begins. This solution has the disadvantage of shortening EWO duration, which in turn could lead to an incomplete removal of carbon dioxide from the mechanical dead space. The third approach consists of reducing the extrinsic PEEP by an amount equivalent to EWO-induced auto-PEEP. Further studies are needed to compare the risks and benefits of these different options in patients with severe ARDS.

Effects of Expiratory Washout on Hemodynamics and Arterial Oxygenation

During permissive hypercapnia combined with EWO, $P_{a_{CO_2}}$ increased significantly by 44% and true pulmonary shunt decreased by 24%. Except in two studies, most authors found no significant influence of TGI on $P_{a_{CO_2}}$. In the present study, a strong correlation was found between increase in $P_{a_{CO_2}}$ and mean airway pressure, suggesting that EWO-induced improvement in arterial oxygenation was mainly related to the auto-PEEP effect.

Again, this difference from previous studies is likely explained by the high EWO flow rate that we used. Expiratory washout also induced significant hemodynamic effects characterized by a decrease in cardiac index, heart rate, mean pulmonary artery pressure, and right ventricular stroke work index along with increases in systemic vascular resistance index, arteriovenous oxygen difference, and oxygen extraction ratio. It is likely that these changes resulted from EWO-induced relief of the hyperadrnergic state after the decrease in $P_{a_{CO_2}}$, and also from the EWO-induced increase in airway pressures. Two different mechanisms probably contributed to decreased cardiac index and heart rate: $P_{a_{CO_2}}$ reduction and normalization of pH reduced carbon dioxide-induced systemic vasodilation and catecholamines release, and auto-PEEP decreased venous return. The observed decrease in pulmonary artery pressure may have been a balance between two opposite effects—pulmonary arterial vasodilation induced by an increase in pH and reduction in $P_{a_{CO_2}}$ and an increase in pulmonary arterial pressure resulting from the increase in mean airway pressure. The former effect was more predominant than the latter. Finally, EWO-induced hemodynamic effects were more beneficial than detrimental, suggesting that the relief of hypercapnia-induced hyperadrenergic tone was largely predominant over the deleterious hemodynamic consequences of an EWO-induced increase in airway pressure.

In conclusion, this study shows that, when used with a pre-equipped ventilator and a specific endotracheal tube rendering unnecessary the placement of tracheal catheter, EWO is an easy-to-use and effective method for reducing $P_{a_{CO_2}}$, increasing pH, and reversing deleterious hemodynamic effects of permissive hypercapnia, such as increased true pulmonary shunt, tachycardia, and increased mean pulmonary arterial pressure. However, these beneficial effects, obtained with an EWO flow rate of 15 l/min, are countered by an increase in airway pressure related to auto-PEEP resulting from expiratory flow limitation. In the future, if EWO is used for patients with severe ARDS in whom a pressure- and volume-limited strategy is indicated, manual or automatic systems that allow easy measurement of auto-PEEP at the bedside should be included in the ventilator.

The authors thank Dr. P. Cluzel, Dr. L. Bodin, and Dr. P. Poite for their direct participation in the study; the nurses of the surgical intensive care unit for their full cooperation; the medical students of the surgical intensive care unit for their valuable help; and Véronique Connan for her secretarial assistance.

References

2. Gattinoni L, Pesenti A, Bombino M, Baglioni S, Rivolta M, Rossi

Anesthesiology. V 87. No 1, Jul 1997


